Extensive white matter lesions after 2 years of fingolimod: progressive multifocal leukoencephalopathy or MS relapse?

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Manuscript type:

Numbers of characters in the title: 119 characters

Words count in the main body of the manuscript: 875

Words count in the abstract: 97

Words count in the legend: 133

Number of references: 10

1 color figure

Keywords: multiple sclerosis - fingolimod - progressive multifocal leukoencephalopathy - MRI

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Abstract

Fingolimod is a widely used treatment for highly active relapsing multiple sclerosis (RR MS). Here we report the case of a 27-year-old MS patient treated for more than two years by fingolimod, who presented severe hemiplegia and speech disturbances associated with extensive white matter lesions on brain MRI. Although initial presentation questioned the possibility of progressive multifocal leukoencephalopathy, final diagnosis was MS relapse and appropriate treatment resulted in clinical and radiological improvement. Severe MS relapses under fingolimod have been reported, but late onset after treatment initiation and extensive subcortical topography are unusual, and represent a diagnostic challenge.

Introduction

Fingolimod (Gilenya®, Fg), the first-in-class orally compound that has shown efficacy in clinical trials for the treatment of relapsing-remitting multiple sclerosis (RR MS), is used as a first line therapy for highly active RR MS or as a second line therapy(1). Fg is a sphingosine 1-phosphate partial agonist that downregulates expression of S1P receptors on lymphocytes, preventing their recirculation from lymph nodes. Its administration results in a decrease of circulating T and B lymphocytes. Tumefactive MS lesions have been described under Fg, leading to the consideration that it may have a paradoxical effect in some cases (2). Moreover, 5 cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in association with Fg, highlighting the need for cautious monitoring.

We report the case of a 27-year-old female who presented a severe MS relapse associated with two atypical extensive subcortical lesions mimicking PML, occurring under Fg, 24 months after treatment onset.

Case Report

A 27-year-old female with a 6 year-history of RR MS was admitted in our Department in July 2015. Because of persisting clinical relapses and radiological activity under first line Disease Modifying Therapy, she was switched to Fg in June 2013. One month after, she reported a mild relapse, then remained asymptomatic (EDSS 0). In July 2015, more than two years after Fg onset, she developed, within a few days, a right-sided hemiplegia with severe speech disturbance. Brain MRI (performed 7 days after symptom-onset) revealed two new large subcortical white matter lesions (figure: A-H). The radiological aspect of the lesions with large size, irregular borders and partial involvement of U-fibers, and their occurrence under

Fg, were atypical for MS lesions. The presence of a strong peripheral hyperintensity on Diffusion Weighted Imaging (DWI), associated with an Apparent Diffusion Coefficient (ADC) restriction over 40%, and a faint peripheral enhancement after gadolinium injection, was suggestive of PML (figure: A-H). Fg was immediately stopped. Blood JC Virus (JCV) serology was negative (controlled twice). CSF analysis was normal; PCR for JCV in CSF was negative. PML was therefore excluded and the patient received IV methylprednisolone (IVMP) during 10 days. At day 15, brain MRI revealed an extension of the left subcortical white matter lesion, while ADC restriction was less visible, and areas of contrast enhancement had regressed (figure: I - Q). At day 21, lesions were unchanged but ADC was normalized (not shown). In August 2015, she had a new relapse with a cerebellar ataxia, right-sided facial hypoesthesia and left-sided hypoesthesia. EDSS was of 6.0. Brain MRI showed a new extensive lesion of the right middle cerebellar peduncle (not shown); the previous lesions were unchanged. She received IVMP and natalizumab (Nz) was initiated in October 2015. She progressively clinically improved, with an EDSS of 3.0 after 6 months of Nz treatment. Follow-up MRI showed a complete regression of DWI hyperintensities and the absence of contrast enhancement (figure: R - W).

Discussion

This case shows the complexity to reach a diagnosis in the case of extensive encephalic lesions appearing 2 years after Fg initiation.

Given the severity of the neurological symptoms (hemiplegia and speech disturbance) and the radiological aspect of the lesions (large size, irregular borders, involvement of some U-fibers, peripheral DWI hyperintensity with ADC restriction and marginal contrast enhancement (3)), PML was the first hypothesized diagnosis. Even if few PML cases have been described with

Fg, prescription and follow-up guidelines do not include JCV serology, and the unknown status of our patient at first reinforced the suspicion for this diagnosis. PML was finally ruled out by the negativity of JCV serology and the JCV-PCR in the CSF. However, these viral results are not immediately available; in addition, a recent PML case has been diagnosed in an MS patient despite a negative JCV serology 2 weeks after the onset of symptoms (5). Concerning ADC, which is known to be reduced in PML lesions, decrease (up to 66%) in the very early phase of acute MS lesions has been documented, especially in the first 7 days (with a maximum of 10 days) after symptom onset (4). This radiological finding is thus not completely specific of PML.

Severe MS relapses under Fg have been reported in particular situations: i) during a switch between natalizumab to Fg (6), ii) after Fg cessation, as a rebound effect (7), and iii) during the first 5 months of treatment, which can be equivalent to a lack of efficacy or even questions a paradoxical effect (2, 8). Hellman et al (9) reported a case of tumefactive demyelination, beginning 14 months after Fg treatment onset, with a diagnosis of typical demyelination on brain biopsy performed 22 months after Fg initiation. Our case is, to our knowledge, the first report of extensive subcortical lesions after 24 months of well-conducted treatment with Fg. The long clinical and radiological stability before a spectacular aggressive activity of MS disease questions the physiopathology of such disease "rebound". Although mechanisms involved in such aggressive MS relapses are unknown, the presence of neutralizing antibodies against Fg, in analogy with those described against natalizumab(10) might be hypothesized.

Cautious monitoring is needed for MS patients with Fg, even after 2 years of well-conducted and well-tolerated treatment. This case also emphasizes the relevance of a precise description of such extensive subcortical lesions and their evolution in order to differentiate MS relapse from PML, hence optimize therapeutic strategy.

Legend

Brain MRI:

Brain MRI performed at day 7 (A-H); day 15 (I-Q) and at month 7 (R-W) of symptoms onset (D0).

From left to right column: Fluid-Attenuated Inversion Recovery sequences (A, E, I, N, R, U), T1 sequences with contrast (B, F, K, O, S, V), Diffusion-Weighted sequences (C, G, L, P, T, W), and Apparent Diffusion Coefficient maps (D, H, M, Q).

MRI at D7 shows extensive lesion of left frontoparietal and right parietal white matter, hyperintense on FLAIR with punctate, irregular margins (A&E), midly hypointense on T1 with a faint peripheral enhancement (B&F,yellow arrows), a strong hyperintensity on DWI (C&G) and an ADC decrease over 40% (D&H,red arrows). Subcortical U-fibers are partially involved. MRI at D15 shows extension of FLAIR and DWI hyperintensity but regression of contrast enhancement (K&O) and partial regression of ADC restriction (M&Q). MRI at M7 shows complete regression of DWI high signal and no contrast enhancement.

Disclosures

Dr Boudot de la Motte, Dr Bertrand, Dr Reach and Dr Louapre report no disclosure.

Pr Lubetzki reports participation to advisory boards for Biogen, Roche, Genzyme, Novartis, Vertex, with no relation to the submitted work.

Dr Papeix reports participation to meeetings and advisory boards for Teva, Biogen, Novartis, Merck, Genzyme, with no relation to the submitted work.

Dr Maillart reports reports participation to meeetings and advisory boards for Teva, Biogen, Novartis, Merck, Genzyme, with no relation to the submitted work.

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